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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/423,517	02/10/2000	MARCOS DA SILVA FREIRE	3673-2	6833

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EXAMINER	
ZEMAN, ROBERT A	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 05/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/423,517	DA SILVA FREIRE ET AL.	
	Examiner	Art Unit	
	Robert A. Zeman	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *71-80 and 82-96* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *71-80 and 82-96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment and response filed on 12-1-03 is acknowledged. Claims 71,-72, 75-76, 79-80, 82, 84—86, 89 and 92-93 have been amended. Claim 81 has been canceled. Claims 71-80 and 82-96 are pending and currently under examination.

Objections Withdrawn

The objection to claim 84 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn in light of the amendment thereto.

Claim Rejections Withdrawn

The rejection of claim 71 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the term "human use vaccines" is withdrawn in light of the amendment thereto.

The rejection of claims 72 and 86 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the term "capable of" is withdrawn in light of the amendment thereto.

The rejection of claims 75-76 and 89 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the term "said density" is withdrawn in light of the amendment thereto.

The rejection of claims 79 and 92 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the term "an amino acids" is withdrawn in light of the amendment thereto.

The rejection of claims 79 and 92 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the term "at least two of human albumin, a peptide, an amino acid and a protein" is withdrawn in light of the amendment thereto.

The rejection of claim 85 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the phrase "preparing a culture of cells which are permissive to Flavivirus and a cell substrate for the production of human vaccines" is withdrawn in light of the amendment thereto.

Claim Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 71-80 and 82-96 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of producing a vaccine composition comprising propagating Yellow Fever Virus YF17D in chick embryo fibroblasts, does not reasonably provide enablement for methods producing a human vaccine comprising the propagation of any flavivirus other than YF17D on any cell type other than chick embryo

fibroblasts is maintained for reasons of record. The amendment to claims 71 and 80 is insufficient to overcome the instant rejection. The specification still does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims without undue experimentation. Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). A conclusion of lack of enablement means that, based on the evidence regarding each of the applicable factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

The factors include, but are not limited to:

1. The breadth of the claims,
2. The nature of the invention,
3. The state of the prior art,
4. The level of one of ordinary skill,
5. The level of predictability in the art,
6. The amount of direction provided by the inventor,
7. The existence of working examples, and
8. The quantity of experimentation needed to make and/or use the invention based on the content of the disclosure.

Applicant argues:

1. The exemplified use of YF17D is sufficient to teach one of ordinary skill in the art to make and use the presently claimed invention.

2. One of ordinary skill in the art will appreciate from the present description those cells that may be used to culture Flavivirus.

3. The references by Post et al. and Theiler et al. exemplify the level of ordinary skill in the art.

Applicant's arguments have been fully considered and deemed non-persuasive.

The instant claims are drawn to methods of producing a human flavivirus vaccine comprising the propagation of a flavivirus in permissive cells wherein said cells are initially seeded at a density of less than $2x10^5$ cells/cm^2 and infected with the seed virus at a multiplicity of infection (MOI) of 0.2-0.0001 infectious units per cell.

With regard to points 1 and 2, the specification provides no guidance as to which flavivirus and cell type other than YF17D and chick embryo fibroblasts could be used in the claimed methods. Moreover, the specification is silent on which flaviviruses are able to infect a given cell type at the claimed MOI. While the specification provides a single working example in which chick embryo fibroblasts are infected with YF17D, it provides no guidelines for extrapolating said working example for use with any other flavivirus or any other cell type. The specification does not provide guidance as to what the cell density should be at the time of infection nor does it provide any guidance as to how the claimed method needs to be adapted for the varying growth rates of differing cell types encompassed by the instant claims. Moreover, as pointed out by Applicant, the prior art would lead one of ordinary skill in the art to use higher cell densities and multiplicities of infection than those used in the claimed methods. While the skill level in arts of cell biology and virology is high, one of ordinary skill in the art would not be able to predict which viruses could be used with a given cell type to produce a productive infection resulting in the production of a human flavivirus vaccine composition utilizing the MOI and cell densities claimed without undue experimentation. Moreover, the specification is silent as to which flavivirus/cell combinations would yield an effective human vaccine. To date, there are

not vaccines for all members of flaviviridae hence one of ordinary skill in the art could not contemplate which flavivirus/cell combinations would yield an effective vaccine.

With regard to Point 3, said references are not commensurate in scope with the claimed invention (i.e. are limited to yellow fever viruses) nor do they utilize the same method steps those of the instant invention. Therefore, one cannot extrapolate any conclusions drawn in the cited references to the claimed invention. Moreover, since Applicant failed to point specifically, what portions of the cited references supported his traversal of the instant rejection, any arguments predicated on said references are deemed non-persuasive.

Therefore, given the lack of success in the art, the lack of working examples, and the unpredictability of the generation of a productive flavivirus infection in a given cell type, the specification, as filed, is not enabling for methods producing a human vaccine comprising the propagation of any virus other than YF17D on any cell other than chick embryo fibroblasts.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 71-96 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejection of claims 71 and 85 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the claim language used in step (b) of the claimed method is maintained for reasons of record. Contrary to Applicant's assertion to the contrary, one of skill in the art would not be able to measure and adjust the cell density of culture as recited in the instant claims. The units **cells/cm^2** are used to describe cell densities of adherent cell cultures, whereas cells/ml are the units used for suspension cultures. Consequently it is unclear how the claimed cell density of "less than $2x10^5$ cells/cm^2" applies to cultures. It should be noted that amended dependent claims 75-76 and 89 also recite this language.

The rejection of claims 71 and 85 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the claim language used in step (d) of the claimed method is maintained for reasons of record. The amendment to said claims is insufficient to overcome the rejection. The method claims, as amended are confusing. If the cells are in a suspension culture, removing the medium also removes the cells (a separation step is lacking). Moreover, the cell "collection" of step (d) is never refed with culture medium and hence would not be able to survive 144 hours. Moreover, step (f) makes no sense since there is no culture medium to remove from the second incubated cell culture (all culture medium was removed in step (d). Additionally, it should be noted that while step (d) recites the inoculation of the claimed cells with 0.2-0.0001 infectious units per cell, it is unclear what the cell density of the culture is when infected.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (571) 272-0866. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert A. Zeman
May 19, 2004

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